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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,363	LAWLOR ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11-14,18,22,29-32 and 36* is/are pending in the application.

4a) Of the above claim(s) *22,29-32 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,11-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/23/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14/05,06/08/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-5, 8, 11-14, and 18) in the reply filed on 18 October 2007 is acknowledged. The traversal is on the ground(s) that the lack of unity of invention should not rely on the evaluation of novelty (Remarks, p. 3, second paragraph). Applicant argues that the present claims, when considered as a whole, define a contribution over the prior art (Remarks, p. 3, last paragraph). Applicant also argues that a determination to make the pending restriction requirement final must evidence the patentable distinctness of all four groups, one from the other (Remarks, p. 4, first paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

The instant application is filed under 35 USC 371 as the national stage of an international application. Pursuant to 37 CFR 1.475, a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention "). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," **should be considered with respect to novelty and inventive step**. For example, a document discovered in the search shows that there is a presumption of lack of novelty or inventive step in a main claim, so that there may be no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept (MPEP 1850 subpart II, Determination of "Unity of Invention"). In the instant case, the inventions listed as Groups I-IV in the Requirement for Restriction/Election mailed 8/22/2007, do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: claim 1 is anticipated by US Patent 5,449,515 (12 September 1995). The '515 patent teaches the administration of IL-4, which decreases the level of expression of G-CSF in a method of treating arthritis (column 5, lines 10-15; claims 1, 11, and 12). The '515 patent teaches all of the limitations of claim 1. As such, the remaining claims lack the same or corresponding special technical feature in view of the anticipatory art over independent claim 1 and restriction is required. See 37 CFR 1.475 and MPEP 1850.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-5, 8, 11-14, 18, 22, 29-32, and 36 are pending. Claims 6-7, 9-10, 15-17, 19-21, 32-28, 33-35, and 37-45 have been cancelled by Applicant. Claims 22, 29-32, and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 October 2007. Claims 1-5, 8, 11-14, 18 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 14 November 2005 and 8 June 2007 have been fully considered. Signed copies are attached.

Specification - Objections

4. The disclosure is objected to because of the following informalities: the last paragraph of page 32 is difficult to read. It is unclear whether this is a printing error in the original submission or a scanning error. Applicant is requested to provide a readable copy of the last paragraph of page 32.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method of Treatment of Arthritis Using inhibitors of G-CSF or G-CSFR.

Claim Objections

6. Claims 11-14 are objected to because of the following informalities: dependent claims 11-14 recite the term "antagonist." Independent claim 1 does not recite the term "antagonist" but does recite "an agent which inhibits the activity or level of expression of…" which is understood to be an antagonist. For purposes of clarity, consistency in claim language is requested.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis comprising administering a polypeptide or small molecule agent which inhibits the activity or level of expression of G-CSF or G-CSFR, does not reasonably provide enablement for a method of treating arthritis comprising administering an agent is a DNA or RNA antagonist and comprises a sense or antisense polynucleotide sequence or a genetic sequence encoding G-CSF or G-CSFR, which reads on **gene therapy**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant claims are drawn to a method of treating arthritis comprising administering a polypeptide or small molecule agent which inhibits the activity or level of expression of G-CSF or G-CSFR The instant rejection is primarily concerned with the claims as they are drawn to claims 1 and 18, where the patient is administered a composition comprising DNA or RNA and comprises a sense or antisense polynucleotide sequence or a genetic sequence encoding G-CSF or G-CSFR. Claim 18, is drawn to a method of gene therapy.

The level of skill of those in the art is high due to the unpredictability of using DNA, RNA, sense or antisense polynucleotides as agents which inhibit the activity or level of expression of G-CSF or G-CSFR.

9. Both the art and the instant specification support the use of various agents to suppress the level of expression or to inhibit the activity of to inhibit the level of expression of G-CSF. Hamilton et al., (US Patent 5,449,515, 12 September 1995) teaches a method of treating inflammatory disorders, including rheumatoid arthritis, comprising administering IL-4 for decreasing the production (level of expression) of G-CSF (column 5, lines 3-15; claims 1, 11, and 12) (compare instant claim 1). Devalaraja et al., US Patent Application Publication 20070059280 (15 March 2007, benefit to 20 March 2000) teach that G-

CSF synergistically enhances the chemoattractant effects of IL-8 on the recruitment of neutrophils. Because IL-8 is a key mediator of inflammatory diseases, it would be desirable to identify substances capable of inhibiting the synergistic interactions of CSFs and chemokines for use in the treatment of diseases responsive to this inhibition, including rheumatoid arthritis in mammals (paragraph 13). The '280 publication also teaches a method of treating inflammation or an autoimmune disease comprising administering to a mammal in need thereof a therapeutically effective amount of an inhibitor of a G-CSF which inhibits inflammation or autoimmune disease (paragraph 36; claims 12 and 16).

However, claim 1 (in the alternative) and dependent claim 18 read on gene therapy. Gene therapy as a means of treatment is unpredictable (see, Juengst, BMJ. 2003 Jun 28;326(7404):1410-1). The art does not teach administration of DNA or RNA comprising a sense or antisense polynucleotide sequence to a mammal or human for the treatment of arthritis.

The instant specification only provides general information, but not substantial guidance on the use of gene therapy and vectors (p. 20, line 16 to page 22, line 17 - general definitions). Generic vectors are taught as "viral vectors" at page 29, lines 13-18 and page 30, lines 14-19. The preferred vector, as DNA , is taught at p. 31, line 1. DNA incorporation into a cell is generally taught by electroporation (p. 31, line 4), liposome fusion (p. 31, line 4), and nuclear microinjection (p. 31, line 6). However, these three means are *in vitro* methods of transferring DNA into a cell. The specification does not teach *in vivo* transfer of DNA or RNA at all, whether in sense or antisense polynucleotide, for the treatment of arthritis. The instant claims are drawn to the treatment of subjects, which requires *in vivo* treatment methods. The lack of guidance in the specification as to how to make or use DNA, RNA, sense/antisense polynucleotides in an *in vivo* method of treating arthritis amounts to nothing more than an invitation to experiment. No working examples of *in vivo* gene therapy are set forth in the instant specification for DNA or RNA comprising sense or antisense polynucleotide sequences. Although working examples are not required, they are helpful in demonstrating that Applicant has sufficiently taught how to make and use the invention without undue experimentation. Without including fundamental guidance as to how to make and use the claimed method in the alternative embodiment of gene therapy, one of skill in the art would not be able to practice the claimed method without undue experimentation.

The claims recite administering DNA and RNA as a sense or antisense polynucleotide, but neither the specification nor the claims teach any specific nucleic acid sequence. Gene therapy is still in its infancy and, as such, is very unpredictable. Administration of nucleic acids for gene therapy is highly dependent on a number of distinct factors, including the bioavailability of the pharmaceutical formulation, the nature of the condition being treated, and the overall health of the subject. There are many well-

documented problems associated with gene therapy, including inefficient gene transfer, host immune response, and the need for tissue-specific targeting (see Chung-Faye *et al.*, Mol Med Today. 2000 Feb (6):82-87, especially at p. 86, column 2, second paragraph; and Verma, *et al.*, Nature. 1987 Sep 18;389:239-242, especially p. 239, third column, first full paragraph). Both Chung-Faye *et al.*, and Verma *et al.*, teach that gene therapy as a means of treatment, is known to be unpredictable.

Chen et al, (Transplant Immunology. 2002;9:301-314) teaches that a variety of barriers exist to efficient targeted expression by gene therapy vectors (p. 306, column 1). In order to achieve this goal vectors must selectively reach and be retained by the target tissue, enter cells and negotiate endosomal compartments ands vector-derived nucleic acid must be transported to the nucleus and must be efficiently transcribed (p. 306, column 1). Chen et al, further notes that host innate and adoptive immune responses to vector components and transgene products limit vector expression through apoptosis, T-cell mediated cytotoxicity, vector clearance and inhibition of transcription (p. 306, column 1). In addition, whether an individual cytokine promoter inhibits or augments transgene expression may also be determined by vector promoter structure, for example, the deletion or mutation of a transcription factor binding site may lead to loss of inhibition by a given cytokine and precise characterization of the interactions between cytokines and promoter elements may ultimately lead to gene therapy vectors with promoters designed to capitalize on the cytokine milieu of the target tissue, resulting in augmentation of expression rather than attenuation (p. 309, column 2, to p. 310, column 1). Romano (Drugs, News Perspect. 2003;16(5):267-276) teaches that vector design is only beginning to address several pressing issues in the transfer of gene delivery improvement, stabilization of transgene expression and safety (abstract). Romano, further teaches that the degree of vector development is still not sufficiently adequate to successful applications in therapy (p. 268, column 3) and transgene silencing is often observed *in vivo* and constitutes one of the biggest obstacles for gene therapy programs (p. 272, column 3). Deonarain (Expert Opin Ther Pat. 1998;8:53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Instant claim 18, in the alternative, also reads on the method of treating arthritis wherein the antagonist is DNA or RNA and comprises a genetic sequence encoding G-CSF or G-CSFR. This alternative embodiment reads on a DNA/RNA vaccine.

The specification does not teach how to make or use a G-CSF or G-CSFR DNA/RNA vaccine. There are no working examples of a G-CSF or G-CSFR DNA/RNA vaccine set forth in the instant specification. Tait et al. (Clin.Canc.Res. 1999 Jul;5:1708-1714) teach the unpredictability of DNA

vaccines in the clinical setting. The authors' prior phase I trial of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant (LXSN-BRCA1sv) demonsrated vector stability, minimal immune response, gene transfer and expression, and some tumor reduction in the patients (p. 1708, column 2, second paragraph). In contrast, the Phase II trial inititiated in pateints with stage III and IV grade ovarian cancer, showed a high preponderance for vector instability (vector was degraded rapidly), a rapid immunological response invoking neutralizing antibodies to the retroviral vector, and no clinical response to the therapy. Although the difference in response to the therapy may be attributed to differences in immunocompetence between the phase I and II patients (p. 1712, column 2), the end results indicated that further experimentation is necessary prior to the successful application of DNA vaccines. A person of skill in the art would not be able to make or use a G-CSF or G-CSFR DNA/RNA vaccine without undue experimentation.

Therefore, based on the discussions above concerning the art's recognition that gene therapy and DNA vaccines are unpredictable, the specification fails to teach the skilled artisan how to make and use the claimed methods of gene therapy to treat arthritis without resorting to undue experimentation. Due to the large quantity of experimentation necessary to determine how to make and use the claimed method of gene therapy to treat arthritis, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that gene therapy and DNA/RNA vaccines are unpredictable, and the breadth of the claims which fail to recite specific vectors, nucleic acid sequences, or any method steps related to gene therapy, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-3, 5, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamilton et al., US Patent 5,449,515 (12 September 1995).

The claims recite a method of treatment of arthritis comprising administering to the subject an effective amount of an agent which inhibits the activity or level of expression of G-CSF or G-CSFR.

The '515 patent teaches a method of treating inflammatory disorders, including rheumatoid arthritis, comprising administering IL-4 for decreasing the production (level of expression) of G-CSF (column 5, lines 3-15; claims 1, 11, and 12) (compare instant claims 1-3). Administration of the composition to a human or animal subject is taught at column 2, lines 60-61 (compare instant claims 5 and 8).

12. Claims 1-5, 8, and 11-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Devalaraja et al., US Patent Application Publication 20070059280 (published 15 March 2007, benefit to 20 March 2000), as evidenced by Luross et al., (Immunology. 2001 Aug;103(4):407-16, Abstract only).

The claims recite as stated above. The '280 publication teaches a method of treating inflammation or an autoimmune disease comprising administering to a mammal in need thereof a therapeutically effective amount of an inhibitor of a G-CSF which inhibits inflammation or autoimmune disease (paragraph 36; claims 12 and 16) (compare instant claims 1, 2, and 5). Treatment of rheumatoid arthritis is taught at paragraph 42 and claim 18 (compare instant claim 3). Inhibitors of G-CSF and G-CSFR which inhibit activation or antagonists of G-CSF and G-CSFR, including antibodies (paragraph 31) and monoclonal antibodies (paragraphs 32 and 88) (compare instant claims 1 and 11-13). Administration of anti-G-CSF antibodies to a human are taught at paragraph 106 (compare instant claim 8). Administration of soluble G-CSFRs which prevent interaction with naturally-occurring receptors is taught at paragraphs 107 and 111 (compare instant claim 14). The '280 publication defines autoimmune diseases to include those with anti-collagen antibodies, thereby encompassing collagen-induced arthritis (paragraph 101) (compare instant claim 4). It is also old and well-known in the art that collagen-induced arthritis is an animal model of human rheumatoid arthritis (see, for exemplary purposes only, Luross et al., Immunology. 2001 Aug;103(4):407-16, Abstract only) (stating "[c]ollagen-induced arthritis has also been the model of choice in terms of testing potential new therapeutic agents for the treatment of human RA.") (compare instant claim 4).

Conclusion

13. The prior art made of record and not presently relied upon is considered pertinent to applicant's disclosure.

Devalaraja et al., US Patent 7,108,852 (19 September 2006, benefit to 20 March 2000) (published as US Patent Application Publication 20020141994, 3 October 2002, benefit to 20 March 2000) teaches the same subject matter as Devalaraja et al., US Patent Application Publication 20070059280 (15 March 2007, benefit to 20 March 2000) cited above.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Examiner, Art Unit 1647